sumption coagulopathy occurred, the latter contributing to the growth of the thrombus and, therefore, to worsening of the heart failure.

The precise processes by which the defibrination disorders are induced are only partially understood. However, some factors that can be present in a low cardiac output state such as regional tissue ischemia, stagnant blood flow, increased endogenous alpha-adrenergic activity and hepatic dysfunction may predispose a patient such as ours to the development of consumption coagulopathy.[10,11]

To what extent the coagulation disorder contributed to this patient's death is uncertain. From the findings at autopsy, however, it was clear that the bulk of the left ventricular thrombus developed acutely. Death was due to severe left ventricular failure with pulmonary edema and low cardiac output, at least partially due to compromise of the left ventricular chamber volume by the massive mural thrombus. Early administration of heparin may have been beneficial in preventing the growth of the mural thrombus. A noninvasive diagnosis before the patient died may have been possible by means of iodine 125 fibrinogen scanning or cross-sectional echocardiography.[12] The recognition that a consumption coagulopathy may occur in association with the development of mural thrombi in patients with congestive heart failure may lead to earlier diagnosis and more definitive therapy.

Summary

The association of congestive heart failure, cardiac mural thrombosis and consumption coagulopathy is not generally recognized. A case of consumption coagulopathy in the setting of congestive heart failure and massive left ventricular mural thrombosis is described. A 55-year-old man was admitted to hospital with symptoms resulting from congestive heart failure. Abrupt deterioration in his hemodynamic status was associated with development of consumption coagulopathy and rapid enlargement of a left ventricular mural thrombus, noted only at postmortem examination. Possible pathophysiologic mechanisms are discussed. Recognition that consumption coagulopathy can occur in this setting may allow earlier diagnosis and definitive anticoagulant therapy of mural thrombosis in congestive heart failure.

REFERENCES

1. Rapaport SI: Defibrination syndromes, *In* Williams WJ, Beutler E, Erslev AJ, et al (Eds): Hematology, 2nd Ed. New York, McGraw-Hill Inc, 1977, p 1455

2. McKay DG: Disseminated Intravascular Coagulation. New York, Harper and Row, 1965

3. Attar S, Hanashiro P, Mansberger A, et al: Intravascular coagulation—Reality or myth? Surgery 68:27, 1970

4. Bergentz SE, Leandoer L: Disseminated intravascular coagulation in shock. Ann Chir Gynaecol 60:175, 1971

5. ten Cate JW, Timmers H, Becker AE: Coagulopathy in ruptured or dissecting aortic aneurysms. Am J Med 59:171, 1975

6. Bigger R, Vreeken J, Stibbe J, et al: Arterial aneurysm as a cause of consumption coagulopathy. N Engl J Med 285:152, 1971

7. Rosenberg N, Zullo RJ: Massive venous thrombosis with incoagulability of the blood. Arch Surg 76:981, 1958

8. Favara BE, Franciosi RA, Butterfield LJ: Disseminated intravascular and cardiac thrombosis of the neonate. Am J Dis Child 127:197, 1974

9. Ikematsu S, Itoh O, Samori T, et al: A case of consumption coagulopathy due to atrial giant thrombus. Jpn J Clin Hematol 16:530, 1975

10. Ratnoff OD: The hemostatic defects of liver disease, *In* Ogston D, Bennett B (Eds): Hemostasis: Biochemistry, Physiology, and Pathology. New York, John Wiley and Sons, 1977 pp 446-466

11. McKay DG, Latour JG, Pannish MH: Activation of Hageman factor by alpha-adrenergic stimulation. Thromb Diath Haemorrh 23:417, 1970

12. De Maria AN, Neumann A, Bommer W, et al: Left ventricular thrombi identified by cross-sectional echocardiography. Ann Intern Med 90:14, 1979

Refer to: Hubbell FA, Weber MA, Megaffin BB, et al: Acute renal impairment produced by a uricosuric diuretic. West J Med 133:444-446, Nov 1980

Acute Reversible Renal Impairment Produced by a Uricosuric Diuretic

F. ALLAN HUBBELL, MD
MICHAEL A. WEBER, MD
BERNARD B. MEGAFFIN, MD
DEBORAH D. BREWER, RN
Long Beach, California

TICRYNAFEN (2, 3-dichloro-4-[2-thienylcarbonyl]-phenoxy-acetic acid) is a uricosuric diuretic that lowers blood pressure by a mechanism similar to that of thiazide diuretics. A theoretical advantage of uricosuric diuretics is their ability to reduce rather than elevate serum uric acid levels. Although ticrynafen was recently withdrawn from general use by its manufacturer for evaluation of possible hepatotoxicity, experience with uricosuric compounds may have relevance for future therapeutic strategies. In this report we discuss two cases in which there were abrupt increases in

From the Veterans Administration Medical Center, Long Beach, California, and the Department of Medicine, University of California, Irvine (Drs. Hubbell and Weber).

Submitted, revised, March 6, 1980.

Reprint requests to: Michael A. Weber, MD, Hypertension Center (W130), VA Medical Center, 5901 E. 7th St., Long Beach, CA 90822.

blood urea nitrogen and creatinine concentrations soon after the institution of ticrynafen therapy.

Reports of Cases

PATIENT 1. A 66-year-old white man had a four-year history of essential hypertension controlled by hydrochlorothiazide (100 mg a day) and clonidine (0.4 mg a day). There was no history of renal, hepatic or cardiac disease. Findings on physical examination were unremarkable except for early nonexudative fundoscopic changes. Three weeks after cessation of all medications he was given ticrynafen (250 mg a day) and instructed to drink as much liquid as possible for the first three days of therapy. Blood pressure without treatment was 151/97 mm of mercury with the patient lying down and 159/101 mm of mercury standing. The blood urea nitrogen value was 20 mg per dl, the serum creatinine level was 1.1 mg per dl and creatinine clearance was 75 ml per minute. The serum uric acid concentration was 8.2 mg per dl.

After one week of ticrynafen therapy the patient was asymptomatic. The blood pressure was 154/89 mm of mercury when lying down and 158/99 mm of mercury standing. The remainder of the physical examination findings, except for the fundoscopic changes mentioned above, were normal. However, the blood urea nitrogen value had risen to 40 mg per dl, the creatinine level had increased to 2.6 mg per dl and creatinine clearance had fallen to 37 ml per minute. The serum uric acid had fallen to 5.3 mg per dl and the fractional excretion of urate had increased from a baseline of 4 percent to 19 percent. Analysis of urine showed no abnormalities and the 24-hour urine volume was 2,025 ml. There was no eosinophilia. Ticrynafen therapy was discontinued and after three months the patient's blood urea nitrogen and creatinine values returned to baseline (see Table 1).

PATIENT 2. A 49-year-old white man had a 20-year history of hypertension which was being treated with hydrochlorothiazide (50 mg a day), triamterene (100 mg a day), prazosin (2 mg a day) and metoprolol (100 mg a day). Because of an elevation in the serum uric acid concentration, administration of hydrochlorothiazide and triamterene was discontinued and therapy with ticrynafen (250 mg a day) was begun. The patient took his last triamterene and hydrochlorothiazide doses 12 hours before taking the first ticrynafen tablet.

TABLE 1.—*Values for Blood Urea Nitrogen, Serum Creatinine and Uric Acid Concentrations in Two Hypertensive Patients Before, During and After Treatment With Ticrynafen*

	Blood Urea Nitrogen mg/dl	*Creatinine mg/dl*	*Serum Uric Acid mg/dl*
Patient 1			
Pretreatment	20	1.1	8.2
During treatment	40	2.6	5.3
Posttreatment	18	1.1	6.8
Patient 2			
Pretreatment	22	0.9	9.2
During treatment	53	3.8	6.8
Posttreatment	25	1.6	8.2

One week after the institution of ticrynafen therapy the patient complained of general malaise, dry mouth and excessive thirst. Blood pressure was 146/94 mm of mercury lying down and 140/98 mm of mercury standing. The remainder of the physical examination showed no abnormalities. On the previous regimen of diuretics, the blood urea nitrogen value was 22 mg, creatinine was 0.9 mg and serum uric acid was 9.2 mg per dl. After ticrynafen therapy, the blood urea nitrogen level was 53 mg, creatinine was 3.8 mg and serum uric acid was 6.8 mg per dl. Analysis of urine showed no abnormalities and there was no eosinophilia. Three weeks after discontinuation of ticrynafen administration, the blood urea nitrogen value had fallen to 25 mg and creatinine to 1.6 mg per dl; the serum uric acid concentration was 8.2 mg per dl (see Table 1).

Comment

Ticrynafen is a diuretic that, before its withdrawal from general use, appeared appropriate for treating patients with concurrent hypertension and hyperuricemia. The blood pressure lowering effect of the drug is comparable to that of hydrochlorothiazide[1] and chlorthalidone.[2] In addition, the agent inhibits tubular reabsorption of both filtered and secreted urate[3] and thus lowers serum uric acid levels. Adverse effects seen with the use of ticrynafen include occasional weakness, faintness and lethargy. As with other diuretics, postural dizziness can occur.

The two cases presented above illustrate a potentially important adverse reaction that can occur with ticrynafen. One patient was taking a combination of hydrochlorothiazide and triamterene before the institution of ticrynafen therapy. In unpublished studies the combination of ticry-

nafen with the potassium-sparing diuretic triamterene caused an elevation of blood urea nitrogen and serum creatinine up to levels of 81 mg per dl and 5.2 mg per dl, respectively, in three of seven normal volunteers within three days of starting therapy. Although our patient did not take the two drugs concomitantly, the previous triamterene therapy probably played a major role in the abrupt increase in blood urea nitrogen values. There is no obvious explanation for the acute deterioration in renal function associated with ticrynafen in our other patient who had been without treatment for three weeks previously.

The mechanism of the renal impairment induced by ticrynafen is not known. Acute increases in uric acid concentrations in the renal tubule or uric acid-induced interstitial nephritis, although rare,[4] are possible explanations. Fortunately, these apparent reductions in renal function appear to be reversible.

Two additional cases of acute renal failure during ticrynafen treatment have recently been reported.[5,6] In both instances, ticrynafen was substituted for hydrochlorothiazide in the absence of a diuretic-free period for the purpose of rehydration. Clearly, it would be helpful for any previous diuretic treatment to be stopped at least three days before the institution of uricosuric therapy so as to allow sufficient rehydration to minimize the possibility of urate precipitation. Moreover, the future use of uricosuric diuretics should be restricted to hypertensive patients known to be susceptible to clinical gout; administration of these agents for asymptomatic hyperuricemia does not appear to be justified.

REFERENCES

1. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Comparative effects of ticrynafen and hydrochlorothiazide in the treatment of hypertension. N Engl J Med 301:293-297, 1979

2. Hubbell FA, Weber MA, Winer RL, et al: A comparison of the clinical and metabolic effects of chlorthalidone and ticrynafen in hypertension. Clin Pharmacol Ther 27:259, 1980

3. Reese OG, Steele TH: Renal transport of urate during diuretic-induced hypouricemia. Am J Med 60:973-979, 1976

4. Selby T: Acute renal failure from ticrynafen. N Engl J Med 301:1180-1181, 1979

5. Cohen LH, Norby LH, Champion C, et al: Acute renal failure from ticrynafen. N Engl J Med 301:1180, 1979

6. Bennett WM, Van Zee BE, Hutchings R: Acute renal failure from ticrynafen. N Engl J Med 301:1179-1180, 1979